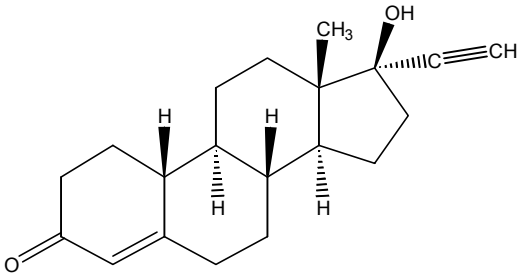
NORETHISTERONE
CAS No. 68-22-4
First Listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Norethisterone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC V.6, 1974; IARC V.21, 1979; IARC S.4, 1982). When administered in the diet, norethisterone increased the incidences of benign liver cell tumors in male mice and male rats and pituitary tumors in female mice and induced benign and malignant mammary tumors in male rats. When administered subcutaneously, the compound induced granulosa cell tumors in ovaries of mice.

There are no data available to evaluate the carcinogenicity of norethisterone in humans (IARC S.4, 1982).

PROPERTIES

Norethisterone occurs as a white, odorless, crystalline powder with a slightly bitter taste. It is practically insoluble in water and nonvolatile oils, slightly soluble in diethyl ether, and soluble in ethanol, acetone, chloroform, dioxane, and pyridine. It is unstable in the presence of air and light. When heated to decomposition, it emits acrid smoke and fumes. Norethisterone is available in the United States as a grade containing 97%-102% active ingredient on an anhydrous basis.

USE

Norethisterone, an orally active progestin, has been used in small amounts in human medicine since 1957 to treat conditions such as amenorrhea, dysfunctional uterine bleeding, endometriosis, premenstrual tension, and dysmenorrhea. Since 1962, the most common use in the United States has been as the progestin in progestin-estrogen combination oral contraceptives. Norethisterone has been used in the treatment of inoperable malignant neoplasms of the breast or as an adjunct to surgery or radiotherapy (IARC V.21, 1979). Norethisterone is also used as an intermediate in the commercial synthesis of norethisterone acetate and possibly in the synthesis of ethynodiol diacetate (IARC V.6, 1974).

PRODUCTION

Chem Sources International indicated that one domestic firm supplies norethisterone (Chem Sources International, 1988). Norethisterone is not produced in the United States. Data on imports were not available. Total U.S. sales for human medicine containing norethisterone have been estimated to have been < 4,400 lb/year prior to 1972 (IARC V.6, 1974).

EXPOSURE

The primary routes of potential human exposure to norethisterone are ingestion, dermal contact, and inhalation. When used as an oral contraceptive, it is usually given in a dose of 0.5-2.0 mg daily in combination with mestranol or ethinylestradiol. It is also used continuously at a daily dose of 0.35 mg in the so-called contraceptive "mini-pill." In its other medicinal uses, norethisterone is given in daily doses ranging from 10 to 30 mg (IARC V.21, 1979). Potential occupational exposure may occur through inhalation or dermal contact for workers involved in the manufacture, formulation, packaging, or administration of norethisterone. In a study carried out in a factory producing oral contraceptives, norethisterone was found in various sectors of the working environment at concentrations ranging from 0.30 to 59.56 $\mu g/m^3$ and in wipe samples from 0.019 to 14.7 $\mu g/cm^3$ (IARC V.21, 1979).

REGULATIONS

Because this chemical is used as a pharmaceutical and in low quantities relative to other chemicals, it is not regulated by EPA. However, there may be a small pollution problem relative to hospital wastes. FDA regulates norethisterone under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription drug approved for human use. FDA has ruled that oral contraceptives for general use must carry patient and physician warning labels concerning use, risks, and contraindications. OSHA regulates norethisterone under the Hazard Communication Standard and as a chemical hazard in laboratories Regulations are summarized in Volume II, Table B-113.